HRAS gene

HRas proto-oncogene, GTPase

Normal Function

The *HRAS* gene provides instructions for making a protein called H-Ras that is involved primarily in regulating cell division. Through a process known as signal transduction, the H-Ras protein relays signals from outside the cell to the cell's nucleus. These signals instruct the cell to grow or divide. The H-Ras protein is a GTPase, which means it converts a molecule called GTP into another molecule called GDP. The H-Ras protein acts like a switch, and it is turned on and off by GTP and GDP molecules. To transmit signals, the protein must be turned on by attaching (binding) to a molecule of GTP. The H-Ras protein is turned off (inactivated) when it converts GTP to GDP. When the protein is bound to GDP, it does not relay signals to the cell's nucleus.

The *HRAS* gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous. The *HRAS* gene is in the Ras family of oncogenes, which also includes two other genes: *KRAS* and *NRAS*. The proteins produced from these three genes are GTPases. These proteins play important roles in cell division, the process by which cells mature to carry out specific functions (cell differentiation), and the self-destruction of cells (apoptosis).

Health Conditions Related to Genetic Changes

bladder cancer

Somatic *HRAS* gene mutations that occur in bladder cells have been associated with some cases of bladder cancer. A particular mutation, the Gly12Val mutation that can cause epidermal nevi (described above), has been identified in a significant percentage of bladder tumors. As a result of this genetic change, the altered H-Ras protein becomes continuously active within the cell. The overactive H-Ras protein directs the cell to grow and divide abnormally, leading to uncontrolled cell division and the formation of a tumor. Mutations in the *HRAS* gene also have been associated with the progression of bladder cancer and an increased risk of tumor recurrence after treatment.

Costello syndrome

At least 15 mutations in the *HRAS* gene have been identified in people with Costello syndrome, a rare condition that affects many parts of the body and increases the risk of developing cancerous and noncancerous tumors. The mutations change single protein building blocks (amino acids) in a critical region of the H-Ras protein. The

most common mutation accounts for more than 80 percent of all cases of Costello syndrome; it replaces the amino acid glycine with the amino acid serine at protein position 12 (written as Gly12Ser or G12S).

The *HRAS* gene mutations that cause Costello syndrome lead to the production of an H-Ras protein that is abnormally turned on (active) in cells throughout the body. Instead of triggering cell growth in response to signals from outside the cell, the overactive protein directs cells to grow and divide constantly. This uncontrolled cell division can result in the formation of noncancerous and cancerous tumors. Researchers are uncertain how mutations in the *HRAS* gene cause the other features of Costello syndrome (such as intellectual disability, distinctive facial features, and heart problems), but many of the signs and symptoms probably result from cell overgrowth and abnormal cell division.

epidermal nevus

Mutations in the *HRAS* gene are involved in the development of abnormal, noncancerous patches of skin called epidermal nevi (singular: nevus). These patches are caused by an overgrowth of cells in the outer layer of skin (the epidermis). *HRAS* gene mutations have been found in a majority of people with a certain type of epidermal nevus called a nevus sebaceous. This type is classified as an organoid epidermal nevus because it involves cells that make up structures (or organs) in the skin, usually the hair follicles, the sweat glands, or the sebaceous glands (glands in the skin that produce a substance that protects the skin and hair). Additional tumors often develop in the region of the nevus sebaceous. In rare cases, these tumors are cancerous. *HRAS* gene mutations are less commonly found in keratinocytic epidermal nevi, a type of epidermal nevus that involves a particular type of epidermal cell called a keratinocyte. Keratinocytic epidermal nevi are not typically associated with additional tumors.

Epidermal nevi are caused by gene mutations that are acquired during the early stages of development before birth. The mutations are present only in the cells of the nevus and not the normal skin cells surrounding it. These changes, which are called somatic mutations, are not inherited. The somatic *HRAS* gene mutations involved in epidermal nevi, change single amino acids in the H-Ras protein. The most common mutation replaces the amino acid glycine with the amino acid valine at protein position 12 (written as Gly12Val or G12V). These mutations lead to production of an H-Ras protein that is always turned on. The affected skin cells grow and divide more than normal cells, resulting in epidermal nevi.

head and neck squamous cell carcinoma

other cancers

Somatic mutations in the *HRAS* gene are probably involved in the development of several additional types of cancer. These mutations lead to a version of the H-Ras

protein that is always active and can direct cells to grow and divide without control. Studies suggest that *HRAS* gene mutations may be common in thyroid and kidney cancers. Increased activity (expression) of the *HRAS* gene has also been reported in other types of cancer.

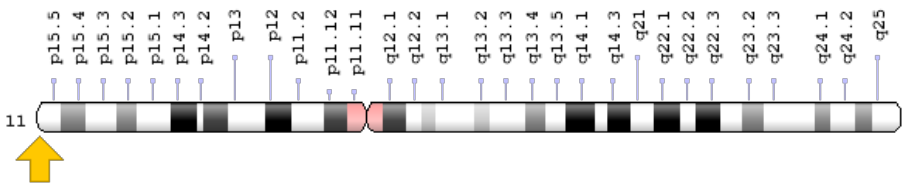
other disorders

Somatic *HRAS* gene mutations are also involved in development of Schimmelpenning syndrome, which is a type of epidermal nevus syndrome. Affected individuals have a type of epidermal nevus called nevus sebaceous (described above) in addition to abnormalities of the brain, eyes, or bones. Problems with these other systems can include seizures, intellectual disability, extra or missing pieces of tissue in eye structures (choristomas or colobomas), underdeveloped bones, and a disorder called rickets that leads to softening and weakening of the bones. Schimmelpenning syndrome is caused by the same gene mutations involved in epidermal nevus. It is thought that the additional signs and symptoms occur because the somatic mutation affects other tissues in addition to the skin.

Chromosomal Location

Cytogenetic Location: 11p15.5, which is the short (p) arm of chromosome 11 at position 15.5

Molecular Location: base pairs 532,242 to 535,567 on chromosome 11 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- C-H-RAS
- Harvey murine sarcoma virus oncogene
- Harvey rat sarcoma viral oncogene homolog
- HRAS1
- Oncogene, G-RAS
- RASH1

- RASH_HUMAN
- Transformation gene: Oncogene HaMSV
- Transforming protein P21/H-RAS-1 (C-H-RAS)
- v-Ha-ras Harvey rat sarcoma viral oncogene homolog

Additional Information & Resources

Educational Resources

- Basic Neurochemistry (sixth edition, 1999): The best characterized small G protein is the Ras family
  https://www.ncbi.nlm.nih.gov/books/NBK28084/#A1424
- The Cell: A Molecular Approach (second edition, 2000): Oncogenes
  https://www.ncbi.nlm.nih.gov/books/NBK9840/

GeneReviews

- Costello Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1507

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28HRAS%5BTIAB%5D%29+OR+%28HRAS1%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- THYROID CANCER, NONMEDULLARY, 2
  http://omim.org/entry/188470
- V-HA-RAS HARVEY RAT SARCOMA VIRAL ONCOGENE HOMOLOG
  http://omim.org/entry/190020

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/HRASID108.html
- Cancer Genetics Web
  http://www.cancerindex.org/geneweb/HRAS.htm
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=HRAS%5Bgene%5D

- HGNC Gene Family: RAS type GTPase family
  http://www.genenames.org/cgi-bin/genefamilies/set/389
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=5173
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/3265
- The Sanger Institute: Catalogue Of Somatic Mutations In Cancer
  http://cancer.sanger.ac.uk/cosmic/gene/analysis?ln=HRAS
- UniProt
  http://www.uniprot.org/uniprot/P01112

Sources for This Summary

- Aoki Y, Niihori T, Kawame H, Kurosawa K, Ohashi H, Tanaka Y, Filocamo M, Kato K, Suzuki Y, Kure S, Matsubara Y. Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nat Genet. 2005 Oct;37(10):1038-40. Epub 2005 Sep 18.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16170316
- Colicelli J. Human RAS superfamily proteins and related GTPases. Sci STKE. 2004 Sep 7; 2004(250):RE13. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15367757
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2828947/
- Estep AL, Tidyman WE, Teitell MA, Cotter PD, Rauen KA. HRAS mutations in Costello syndrome: detection of constitutional activating mutations in codon 12 and 13 and loss of wild-type allele in malignancy. Am J Med Genet A. 2006 Jan 1;140(1):8-16.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16372351
- Giehl K. Oncogenic Ras in tumour progression and metastasis. Biol Chem. 2005 Mar;386(3): 193-205. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15843165
- Gripp KW, Innes AM, Axelrad ME, Gillan TL, Parboosingh JS, Davies C, Leonard NJ, Lapointe M, Doyle D, Catalano S, Nicholson L, Stabley DL, Sol-Church K. Costello syndrome associated with novel germline HRAS mutations: an attenuated phenotype? Am J Med Genet A. 2008 Mar 15; 146A(6):683-90. doi: 10.1002/ajmg.a.32227.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18247425
- Gripp KW, Lin AE, Stabley DL, Nicholson L, Scott CI Jr, Doyle D, Aoki Y, Matsubara Y, Zackai EH, Lapunzina P, Gonzalez-Meneses A, Holbrook J, Agresta CA, Gonzalez IL, Sol-Church K. HRAS mutation analysis in Costello syndrome: genotype and phenotype correlation. Am J Med Genet A. 2006 Jan 1;140(1):1-7.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16329078
- Gripp KW, Stabley DL, Nicholson L, Hoffman JD, Sol-Church K. Somatic mosaicism for an HRAS mutation causes Costello syndrome. Am J Med Genet A. 2006 Oct 15;140(20):2163-9.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16969868

- Groesser L, Herschberger E, Ruetten A, Ruivenkamp C, Lopriore E, Zutt M, Langmann T, Singer S, Klingseisen L, Schneider-Brachert W, Toll A, Real FX, Landthaler M, Hafner C. Postzygotic HRAS and KRAS mutations cause nevus sebaceous and Schimmelpenning syndrome. Nat Genet. 2012 Jun 10;44(7):783-7. doi: 10.1038/ng.2316.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22683711
- Hafner C, Toll A, Gantner S, Mauerer A, Lurkin I, Acquadro F, Fernández-Casado A, Zwarthoff EC, Dietmaier W, Baselga E, Parera E, Vicente A, Casanova A, Cigudosa J, Mentzel T, Pujol RM, Landthaler M, Real FX. Keratinocytic epidermal nevi are associated with mosaic RAS mutations. J Med Genet. 2012 Apr;49(4):249-53. doi: 10.1136/jmedgenet-2011-100637.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22499344
- Kerr B, Delrue MA, Sigaudy S, Perveen R, Marche M, Burgelin I, Stef M, Tang B, Eden OB, O'Sullivan J, De Sandre-Giovannoli A, Reardon W, Brewer C, Bennett C, Quarell O, M'Cann E, Donnai D, Stewart F, Hennekam R, Cavé H, Verloes A, Philip N, Lacombe D, Levy N, Arveiler B, Black G. Genotype-phenotype correlation in Costello syndrome: HRAS mutation analysis in 43 cases. J Med Genet. 2006 May;43(5):401-5. Epub 2006 Jan 27.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16443854
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2564514/
- Levinsohn JL, Tian LC, Boyden LM, McNiff JM, Narayan D, Loring ES, Yun D, Sugarman JL, Overton JD, Mane SM, Lifton RP, Paller AS, Wagner AM, Antaya RJ, Choate KA. Whole-exome sequencing reveals somatic mutations in HRAS and KRAS, which cause nevus sebaceus. J Invest Dermatol. 2013 Mar;133(3):827-30. doi: 10.1038/jid.2012.379. Epub 2012 Oct 25.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23096712
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3556376/
- Oxford G, Theodorescu D. The role of Ras superfamily proteins in bladder cancer progression. J Urol. 2003 Nov;170(5):1987-93. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14532839
- Rauen KA. HRAS and the Costello syndrome. Clin Genet. 2007 Feb;71(2):101-8. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17250658
- Sol-Church K, Stabley DL, Nicholson L, Gonzalez IL, Gripp KW. Paternal bias in parental origin of HRAS mutations in Costello syndrome. Hum Mutat. 2006 Aug;27(8):736-41.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16835863
- Wolff EM, Liang G, Jones PA. Mechanisms of Disease: genetic and epigenetic alterations that drive bladder cancer. Nat Clin Pract Urol. 2005 Oct;2(10):502-10. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16474624

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/HRAS

Reviewed: August 2016
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services